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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,078	11/14/2003	Gunars E. Valkirs	071949-5408	2621

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EXAMINER	
COOK, LISA V	
ART UNIT	PAPER NUMBER
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,078	VALKIRS ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *see attached*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I (claims 1-29) in the reply filed on 11/3/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Amendment Entry

2. Applicant's amendment canceling claims 1-31 and adding new claims 32-38 on 11/3/06 is acknowledged. Applicants contend that new claims 32-38 fall within the elected invention of Group I. Accordingly claims 32-38 are pending and under consideration.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on PTO-1449 has cited the references they have not been considered.

4. The information disclosure statement filed 1/12/04 has been considered as to the merits prior to First Action.

5. The information disclosure statement filed 11/24/04 has been considered as to the merits prior to First Action.

6. The information disclosure statement filed 1/24/05 has been considered as to the merits prior to First Action.

7. The information disclosure statements filed 6/27/05 and 9/6/05 have been considered as to the merits prior to First Action.

8. The information disclosure statements filed 12/8/05 and 1/25/06 have been considered as to the merits prior to First Action.

9. The information disclosure statement filed 4/24/06 has been considered as to the merits prior to First Action.

Drawings

10. No drawings were filed in this application.

Specification

11. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

I. The use of the trademarks has been noted in this application. (.i.e. SEPHAROSE –page 95, and TWEEN-page 96). They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claim Objections

12. Claims 33-38 are objected to under 37 CFR 1.75(c) for the following informalities: The claims are dependent on the method of claim 32, as such they should refer to the previous method by "The". For example claim 33 should read "The method according to claim 32,". Appropriate correction is required.

13. Claims 32-38 are objected to because of the following informalities: Claims 32-38 utilize acronyms (for example see TRAIL, TWEAK, CT, BNP, etc.). Although the terms may have art-recognized meanings, it is not clear if applicant intends to claim any prior art definition of the abbreviations. The terms should be defined in their first instance. For example, BNP is the B-type natriuretic peptide as defined by the disclosure on page 11 section 0034. The initial explanation will convey intended meaning of subsequent abbreviations in the claims. Please define in the claims in order to obviate this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

14. Claims 32-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 32 recites the phrase "fragment thereof", however it is unclear how to define fragments that are considered to relate to the recited markers in the instantly claimed method. The specification does not teach examples of "fragments thereof". The phrase "fragments thereof" is vague and indefinite because the characteristics needed to determine whether an unknown could be considered immunologically detectable while being a "fragment thereof" is unknown. For example, a "fragment thereof" reads on any single amino acid found in the 108 amino acid BNP precursor molecule while the disclosure has not identifies any single amino acid residues that are immunologically detectable in the claimed method. The specification neither discloses a definition for "fragments thereof"", nor does it teach a requisite amount of retained qualities needed or characteristics necessary to determine phrase ""fragments thereof". Accordingly the claims are unclear.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 32-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 32-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 32-38 are drawn to "fragments thereof". The written description is not commensurate in scope with the claims drawn to "fragments thereof". Neither the specification nor the claims teach how to define or obtain "immunologically detectable fragments thereof".

There is no guidance as to what the "fragments thereof" or how much derivation can occur while retaining the required product characteristics necessary to be considered a "fragments thereof", reading on the instant claims. There is no guidance as to what the "fragments thereof" are or which "fragments thereof" can or cannot be used in the method being claimed. The specification does not include structural examples of "fragments thereof".

Thus, the resulting recited "fragments thereof" could result in a complexes not taught and enabled by the specification. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

The skilled artisan cannot envision the detailed structure of the "fragments thereof", thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. An adequate description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules falling within the scope of the claimed genus. Therefore the full breadth of the claims, do not meet the written description provision of 35 USC 112, first paragraph.

16. Claims 32-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to an assay procedure that detects an antibody complex comprising the 108 amino acid BNP precursor or an immunologically detectable fragment thereof. However, the specification does not provide a method wherein the single 108 amino acid BNP precursor or an immunologically detectable fragment thereof is employed to detect stroke (occurrence or nonoccurrence).

In fact, the specification discloses that the measurement of a single marker may have limited use and further teaches that the data relating to levels of various multiple markers for diseased and non-diseased patients may be used to develop a panel of marker indicative of the disease of interest. See page 23 - section 0076 through page 24, for example.

The specification also teaches that BNP is a non-specific marker for neural tissue injury (i.e. stroke). See page 11 sections 0033 and 0034.

Accordingly, it appears that Applicant did not possess the instantly claimed method, at the time the instant application was filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 32-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the measurement of a 4-panel markers in Table 13 on page 105, 7-panel markers in Tables 15 and 16 on page 107, and 8-panel markers in Table 17 on page 108, it does not reasonably provide enablement for any and all marker panel combinations having utility in the determination of stroke in any subject.

Specifically the specification discloses methods involving the measurement of a panel of markers (multiple makers) as a means for assessing stroke (For example see assay design and results – page 105 (Table 13 wherein a 4 marker panel including ***BNP***, capase-3, MMP-9, and vWF-A1 are employed to determine stroke), page 107 (Tables 15 and 16 wherein a 7 marker panel including ***BNP***, caspase-3, NCAM, MCP-1, S100-β, MMP-9, and vWF-intefrin are employed to determine stroke), page 108 (Table 17 wherein a 8 marker panel including ***BNP***, caspase-3, NCAM, MCP-1, S100-β, MMP-9, vWF-A1, and GFAP are employed to measure stroke).

The currently broadly recited claims do not limit the test population and reads on the measurement of various multiple panel markers. However, the claims are directed to the measurement of multiple panel marker combinations that are not taught by the specification to be related to stroke. Accordingly only the marker combinations disclosed in Tables 13, 15, 16, and 17 are enabled (wherein the marker panel comprises BNP).

In order to support the position that the multiple panel marker combination must be specifically taught by the disclosure, the patent to Jackowski et al. (U.S. Patent No. 5,710,008) is herein discussed. Jackowski et al. teach a method comprising analyzing a test sample obtained from a subject for the presence or amount of a plurality of markers selected to identify the presence or absence in the subject of a plurality of conditions comprising myocardial infarction, pulmonary embolism, and congestive heart failure. These markers include ones recited in the instant claims (i.e. CK-BB and cathepsin D). Please see additions markers beginning at column 14 and continuing to column 19.

Jackowski et al. also disclose that the combination of markers must be considered with respect to each in order to diagnosis the specific disorders. See marker diagnostic panels in columns 30-32. These tables show that the absence and or presence of the markers must be evaluated in combination in order to identify the disorder of interest. The instant disclosure only sets forth particular marker combinations that are taught to be specific for stroke. Therefore, only the marker combinations disclosed in Tables 13, 15, 16, and 17 are enabled (wherein the marker panel comprises BNP).

Further, each of the markers is individually taught to be distinguishable in various other disorders. As such the measurement of a single marker or its combination with other markers would not necessarily be indicative of stroke. But vary well may be linked to another disorder taught by the prior art. For example, Gonzalez-Zulueta et al. (US 6,670,138) disclose that caspase-3 activity is known to be increased in such things as epilepsy, Parkinson's disease or Alzhemimer's disease. While, Pandian et al (US 6,627,457) discloses that S-100b (S-10013) is a pregnancy marker (col 3, lines 32-44).

The specification teaches that marker panels must be considered with respect to ROC curves for sensitivity and specificity. Further, the profile of the various marker measurements from a subject must be considered together in order to provide a global probability for stroke. In other words, each marker must be considered and evaluated individually in a subject. See page 9-section 0029, for example.

Although the specification is enabling for the measurement of a panel of markers (multiple makers) as a means for assessing stroke (For example see assay design and results – page 105 (Table 13 wherein a 4 marker panel including ***BNP***, capase-3, MMP-9, and vWF-A1 are employed to determine stroke), page 107 (Tables 15 and 16 wherein a 7 marker panel including ***BNP***, caspase-3, NCAM, MCP-1, S100-β, MMP-9, and vWF-intefrin are employed to determine stroke), page 108 (Table 17 wherein a 8 marker panel including ***BNP***, caspase-3, NCAM, MCP-1, S100-β, MMP-9, vWF-A1, and GFAP are employed to measure stroke), and page 116 section 0266 where various marker combinations are taught to be useful in the detection and distinction of acute stroke and non-acute stroke, it does not reasonably provide enablement for the measurement of stroke (occurrence or nonoccurrence) with a 108 amino acid BNP precursor or an immunologically detectable fragment thereof as a single marker.

Firstly, the claims are drawn to the detection of a 108 amino acid BNP precursor or an immunologically detectable fragment thereof as a measure of stroke. However the specification and prior art teach the measurement of BNP is correlated with various other conditions and/or disorders. In particular, the specification discloses that BNP is useful in blood pressure regulation (see page 81).

The prior art discloses that BNP is indicative of cardiac disease, heart failure, and coronary syndrome (See U.S Patent #6,828,107; Hunt et al. (Clinical Endocrinology, 1997, Vol.47, pages 287-296); Mills et al. (Journal of the American College of Cardiology, Vol.34, No.1, 1999, pages 155-162); and Futterman et al. (American Journal of Critical Care, 2002, Vol. 11, No.2., pages 168-172). Therefore it is not clear how the detection of only BNP in any subject would necessarily be indicative of stroke and not some other condition or disorder.

Secondly, the prior art teaches that no single marker exits for the detection of stroke. More specifically, Diamond et al. (US 2005/0181386) teach that the use of B-type natriuretic peptide or BNP in the assessment of patients with congestive heart failure and dyspnea. Diamond et al. also disclose that the ischemic cascade of glial activation and ischemic neuronal injury in stroke is far more complex and less amenable to the use if a single biochemical marker. Accordingly, no single biochemical marker with the sensitivity and specificity to function independently as a clinical diagnostic marker for stroke exists (see paragraph 0030, for example).

Thirdly, the specification fails to teach the use of a single marker that definitively measures/diagnoses stroke. In fact, the specification discloses that the measurement of a single marker may have limited use and further teaches that the data relating to levels of various multiple markers for diseased and non-diseased patients may be used to develop a panel of marker indicative of the disease of interest. See page 23 - section 0076 through page 24, for example. The specification also teaches that BNP is a non-specific marker for neural tissue injury (i.e. stroke). See page 11 sections 0033 and 0034.

Claim 36 is directed to the measurement of a single BNP marker and the results of a CT scan to determine stroke. However, as discussed a prior the determination of the single BNP marker is not indicative of stroke in any and all subjects. Further, the prior art teaches that the measurement of a CT scan is correlative to screening for brain damage in general groups of patients. See Cala et al. (Medical Journal of Australia, 1980, Vol.2, No.11, pages 616-620, Abstract Only).

The use of CT to distinguish the cause of the brain damage in any subject has not been taught. This position is supported by the instant specification on page 3 - section 0010. The specification discloses that the cause of stroke and the differentiation between ischemic and hemorrhagic is difficult. While CT can detect parenchymal bleeding the measurement of only CT cannot definitively identify stroke. Neither is the combination of CT and BNP indicative of stroke in any subject.

According to Strongin (Laboratory Diagnosis of Viral Infections, Sensitivity, Specificity, and Predictive Value of Diagnostic Tests: Definitions and Clinical Applications, Lennette, e., ed., Marcel Dekker, Inc., New York, pp.211-219, 1992) a number of characteristics need to be considered in the development of any suitable diagnostic assay. These characteristics include the following: (1) the sensitivity of the assay; (2) the true-positive test rate: (3) the false-negative test rate; (4) the specificity, or percentage of patients without the disease who will display a negative result; (5) the true-negative test rate; (6) the false-positive test rate; (7) the predictive value, or the probability that the test result is correctly indicating the presence or absence of the disease; (8) the prevalence, or number of patients in any given population that have the disease in

question; (9) the efficiency or percentage of all results that are true; (10) the accuracy of the recited diagnostic assay.

Additional consideration must also be examined to enable the clinician to practice the invention, including assessment of the following: (1) when is the maximum sensitivity desired? (2) when is the maximum specificity desired?; (3) when is the maximum efficiency desired?; (4) how is the maximum sensitivity or specificity achieved?; (5) how is the predictive value maximized? An essential understanding of these factors is required to enable the skilled artisan to accurately use and interpret any given diagnostic test.

The currently broadly recited claims do not limit the population to be tested and also includes determining the mere presence of the markers. Therefore one of skill in the art would require undue experimentation in order to practice the claimed method measuring a single BNP in the assessment of stroke.

Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 32-38 are provisionally rejected on the ground of nonstatutory double patenting over claims 68-74 of copending Application No. 10/371,149. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: Both applications are drawn to methods measuring the 108 amino acid BNP precursor as an indicator of stroke.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

20. For reasons aforementioned, no claims are allowed.

21. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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